L Number	Hits	Search Text	DB	Time stamp
33	49	Receptor ADJ advanced ADJ glycation	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 14:47
40	5	(US-20020002203-$ or US-20010053357-$ or US-20010039256-$).did. or (WO-9918987-$).did. or (US-20010039256-$ or WO-200020458-$ or WO-200020621-$ or WO-9954485-$ or US-20010053357-$).did.	US-PGPUB; EPO; DERWENT	2003/03/27 14:45
49	4	(Receptor ADJ advanced ADJ glycation) SAME amphoterin	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 14:53
56	15	Morser ADJ Michael ADJ John	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 14:54
63	29	(US-6465422-$ or US-5864018-$ or US-5811401-$).did. or (US-20010039256-$ or US-20020002203-$ or US-20010053357-$ or US-20030059423-$ or US-20030037344-$ or US-20030032663-$ or US-20020177550-$ or US-20020122799-$ or US-20020116725-$ or US-20020106726-$ or US-20020013256-$ or US-20010041349-$).did. or (WO-9918987-$ or WO-9954485-$ or WO-9907402-$ or WO-9822138-$ or WO-9726913-$ or WO-9739121-$).did. or (WO-200020621-$ or WO-200020458-$ or WO-200274805-$ or WO-200230889-$ or US-20020116725-$ or US-20020106726-$ or US-6465422-$ or US-20010039256-$ or US-20010053357-$).did.	USPAT; US-PGPUB; EPO; DERWENT	2003/03/27 14:56
-	18	(Receptor SAME (advanced ADJ glycation)) and RAGE	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/05/16 10:39
-	42	RAGE and (advanced ADJ glycation)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 14:15
-	34	(Receptor SAME (advanced ADJ glycation)) and (cancer or tumor or mata$10 or neoplas$5)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 14:27
-	77	Receptor SAME (advanced ADJ glycation)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 14:45

L Number	Hits	Search Text	DB	Time stamp
13	87	Receptor SAME advanced SAME glycation	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 16:18
20	0	(Receptor SAME advanced SAME glycation) and (extracelular SAME matri$5)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 16:19
27	26	(Receptor SAME advanced SAME glycation) and (laminin fibronectin amphoterin caderin integrin hyaluronic integrin amphoterin)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 16:26
34	104	RAGE and (laminin fibronectin amphoterin caderin integrin hyaluronic integrin amphoterin)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 16:26
-	18	(Receptor SAME (advanced ADJ glycation)) and RAGE	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2002/05/16 10:39
-	42	RAGE and (advanced ADJ glycation)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 14:15
-	34	(Receptor SAME (advanced ADJ glycation)) and (cancer or tumor or mata$10 or neoplas$5)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 14:27
-	77	Receptor SAME (advanced ADJ glycation)	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 16:17
-	49	Receptor ADJ advanced ADJ glycation	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 14:47
-	5	(US-20020002203-$ or US-20010053357-$ or US-20010039256-$).did. or (WO-9918987-$).did. or (US-20010039256-$ or WO-200020458-$ or WO-200020621-$ or WO-9954485-$ or US-20010053357-$).did.	US-PGPUB; EPO; DERWENT	2003/03/27 14:45
-	4	(Receptor ADJ advanced ADJ glycation)SAME amphoterin	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 14:53
-	15	Morser ADJ Michael ADJ John	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2003/03/27 14:54

-	29	(US-6465422-$ or US-5864018-$ or US-5811401-$).did. or (US-20010039256-$ or US-20020002203-$ or US-20010053357-$ or US-20030059423-$ or US-20030037344-$ or US-20030032663-$ or US-20020177550-$ or US-20020122799-$ or US-20020116725-$ or US-20020106726-$ or US-20020013256-$ or US-20010041349-$).did. or (WO-9918987-$ or WO-9954485-$ or WO-9907402-$ or WO-9822138-$ or WO-9726913-$ or WO-9739121-$).did. or (WO-200020621-$ or WO-200020458-$ or WO-200274805-$ or WO-200230889-$ or US-20020116725-$ or US-20020106726-$ or US-6465422-$ or US-20010039256-$ or US-20010053357-$).did.	USPAT; US-PGPUB; EPO; DERWENT	2003/03/27 14:56

(FILE 'HOME' ENTERED AT 16:40:54 ON 27 MAR 2003)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 16:41:02 ON 27 MAR 2003

L1 3464 S (RECEPTOR FOR ADVACNCED GLYCATION ENDPRODDUCT?) OR RAGE
L2 137 S L1 AND (LAMININ OR FIBRONECTIN OR AMPHOTERIN OR CADERIN OR IN
L3 64 DUP REM L2 (73 DUPLICATES REMOVED)
L4 64 FOCUS L3 1-
L5 14 S L4 AND PY<=1998
L6 14 SORT L5 PY

=> d an ti so au ab pi l6 5 6 10 14

L6 ANSWER 5 OF 14 MEDLINE
AN 96029671 MEDLINE
TI The receptor for advanced glycation end products (**RAGE**) is a cellular binding site for **amphoterin**. Mediation of neurite outgrowth and co-expression of **rage** and **amphoterin** in the developing nervous system.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, **(1995 Oct 27)** 270 (43) 25752-61.
Journal code: 2985121R. ISSN: 0021-9258.
AU Hori O; Brett J; Slattery T; Cao R; Zhang J; Chen J X; Nagashima M; Lundh E R; Vijay S; Nitecki D; +
AB The receptor for advanced glycation end products (**RAGE**), a newly-identified member of the immunoglobulin superfamily, mediates interactions of advanced glycation end product (AGE)-modified proteins with endothelium and other cell types. Survey of normal tissues demonstrated **RAGE** expression in situations in which accumulation of AGEs would be unexpected, leading to the hypothesis that under physiologic circumstances, **RAGE** might mediate interaction with ligands distinct from AGEs. Sequential chromatography of bovine lung extract identified polypeptides with M(r) values of approximately 12,000 (p12) and approximately 23,000 (p23) which bound **RAGE**. NH2-terminal and internal protein sequence data for p23 matched that reported previously for **amphoterin**. **Amphoterin** purified from rat brain or recombinant rat **amphoterin** bound to purified sRAGE in a saturable and dose-dependent manner, blocked by anti-**RAGE** IgG or a soluble form of **RAGE** (sRAGE). Cultured embryonic rat neurons, which express **RAGE**, displayed dose-dependent binding of 125I-**amphoterin** which was prevented by blockade of **RAGE** using antibody to the receptor or excess soluble receptor (sRAGE). A functional correlate of **RAGE**-**amphoterin** interaction was inhibition by anti-**RAGE** F(ab')2 and sRAGE of neurite formation by cortical neurons specifically on **amphoterin**-coated substrates. Consistent with a potential role for **RAGE**-**amphoterin** interaction in development, **amphoterin** and **RAGE** mRNA/antigen were co-localized in developing rat brain. These data indicate that **RAGE** has physiologically relevant ligands distinct from AGEs which are likely, via their interaction with the receptor, to participate in physiologic processes outside of the context of diabetes and accumulation of AGEs.

L6 ANSWER 6 OF 14 SCISEARCH COPYRIGHT 2003 ISI (R)
AN 95:201535 SCISEARCH
TI THE RECEPTOR FOR ADVANCED GLYCATION ENDPRODUCTS (**RAGE**) IS A CELL-SURFACE RECEPTOR FOR **AMPHOTERIN** IN THE DEVELOPING CENTRAL-NERVOUS-SYSTEM (CNS) TO PROMOTE NEURITE OUTGROWTH
SO FASEB JOURNAL, (**09 MAR 1995**) Vol. 9, No. 3, Part 1, pp. A382. ISSN: 0892-6638.
AU HORI O (Reprint); CAO R; BRETT J; SLATTERY T; NAGASHIMA M; NITECKI D; MORSER J; STERN D; SCHMIDT A M

L6 ANSWER 10 OF 14 MEDLINE
AN 1999030344 MEDLINE
TI Sp1-binding elements in the promoter of **RAGE** are essential for **amphoterin**-mediated gene expression in cultured neuroblastoma cells.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, **(1998 Nov 20)** 273 (47) 30870-8.
Journal code: 2985121R. ISSN: 0021-9258.

AU Li J; Qu X; Schmidt A M
AB Receptor for AGE (**RAGE**) and the polypeptide **amphoterin** are highly expressed and co-localized in neurons of the developing central nervous system of the rat. In vitro, the interaction of **amphoterin** with neuronal **RAGE** induces neurite outgrowth. We tested the hypothesis that interaction of **amphoterin** with neuronal cells enhances **RAGE** expression, thereby providing a mechanism by which **amphoterin**-mediated regulation of **RAGE** might contribute to promotion of neurite growth and spreading. Incubation of cultured neuroblastoma cells with **amphoterin** resulted in increased transcription and translation of **RAGE**, a process largely inhibited in the presence of anti-**RAGE** IgG but not by nonimmune IgG. To begin to delineate molecular mechanisms underlying these findings, we identified multiple putative binding elements within the 5'-flanking region of the **RAGE** gene for Sp1, a transcription factor that has been critically linked to the process of normal development. DNase I footprinting and electrophoretic mobility shift assays demonstrated multiple functional Sp1-binding sites within the region -245 to -40 of the **RAGE** promoter. Transient transfection of cultured SK-N-SH neuroblastoma cells with chimeric 5'-deletion constructs linked to luciferase reporter revealed that the region containing Sp1-binding elements did not contribute uniquely to basal expression of the **RAGE** gene. Simultaneous mutation of the multiple Sp1-binding elements in this region did not affect basal promoter function; however, promoter responsiveness to **amphoterin** was markedly attenuated. These results point to Sp1-dependent mechanisms underlying **amphoterin**-mediated increases in **RAGE** expression in neuroblastoma cells and further link **amphoterin-RAGE** interaction to development of the nervous system.

L6 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2003 ACS
AN 1997:719241 CAPLUS
DN 128:2367
TI **RAGE**: a receptor with a taste for multiple ligands and varied pathophysiologic states
SO Hormones and Signaling (**1998**), 1, 41-63
CODEN: HOSIFO
AU Schmidt, Ann Marie; Wautier, Jean-Luc; Stern, David; Yan, Shi Du
AB A review with 35 refs. The classical concept of one receptor with specificity and high affinity for only one ligand has evolved considerably. Furthermore, there are apparently accidental but, nonetheless, pathophysiol. relevant ligands, such as intercellular adhesion mol.-1, which interacts with rhinoviruses to facilitate their entry into cells. **RAGE**, a member of the Ig of cell surface mols., shares such properties. **RAGE** interacts with different ligands, with varied implications for cellular functions, depending on the physiol. or pathophysiol. setting. For example, during normal development, **RAGE** interacts with **amphoterin**, a mol. which promotes neurite out-growth. In pathophysiol. states such as diabetes or amyloidosis obsd. in the setting of renal dialysis, **RAGE** binds non-enzymically glycated adducts of macromols. termed Advanced Glycation Endproducts, or AGEs, resulting in perturbation of multiple cellular properties. Alzheimer's disease represents a situation in which **RAGE** expression increases dramatically, and amyloid-beta peptide, thought to be crit. to the pathogenesis of neurodegeneration, is another ligand for **RAGE**. The diverse circumstances in which these varied ligands interact with **RAGE** are the subject of intense investigation to understand the distinct mechanisms that regulate the temporal and spatial expression of this receptor.

=>

L4 ANSWER 1 OF 64 CAPLUS COPYRIGHT 2003 ACS
AN 1999:691229 CAPLUS
DN 131:317761
TI Inhibition of tumor invasion or spreading based on a soluble receptor for advanced glycation endproducts
SO PCT Int. Appl., 88 pp.
CODEN: PIXXD2
IN Schmidt, Ann Marie; Stern, David
AB The present invention provides for a method for inhibiting tumor invasion or metastasis in a subject which comprises administering to the subject a therapeutically effective amt. of a form of sol. receptor for advanced glycation endproducts (**RAGE**). Interruption of cellular **RAGE**-extracellular matrix (**amphoterin** and/or similar structures) interaction appears to be at least one mechanism by which sRAGE limits tumor growth. The present invention also provides a method for evaluating the ability of an agent to inhibit tumor invasion in a local cellular environment which comprises: (a) admixing with cell culture media an effective amt. of the agent; (b) contacting a tumor cell in cell culture with the media from step (a); (c) detg. the amt. of spreading of the tumor cell culture, and (d) comparing the amt. of spreading of the tumor cell culture detd. in step (c) with the amt. detd. in the absence of the agent, thus evaluating the ability of the agent to inhibit tumor invasion in the local cellular environment. The present invention also provides a pharmaceutical compn. which comprises a therapeutically effective amt. of the agent evaluated in the aforementioned method and a pharmaceutically acceptable carrier.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9954485	A1	19991028	WO 1999-US8427	19990416
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6465422	B1	20021015	US 1998-62365	19980417
CA 2325573	AA	19991028	CA 1999-2325573	19990416
AU 9934957	A1	19991108	AU 1999-34957	19990416
EP 1071794	A1	20010131	EP 1999-916699	19990416
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002512038	T2	20020423	JP 2000-544814	19990416
US 2002177550	A1	20021128	US 2001-851071	20010508

L4 ANSWER 2 OF 64 MEDLINE
AN 96029671 MEDLINE
TI The receptor for advanced glycation end products (**RAGE**) is a cellular binding site for **amphoterin**. Mediation of neurite outgrowth and co-expression of **rage** and **amphoterin** in the developing nervous system.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Oct 27) 270 (43) 25752-61.
Journal code: 2985121R. ISSN: 0021-9258.
AU Hori O; Brett J; Slattery T; Cao R; Zhang J; Chen J X; Nagashima M; Lundh E R; Vijay S; Nitecki D; +
AB The receptor for advanced glycation end products (**RAGE**), a newly-identified member of the immunoglobulin superfamily, mediates interactions of advanced glycation end product (AGE)-modified proteins with endothelium and other cell types. Survey of normal tissues demonstrated **RAGE** expression in situations in which accumulation of AGEs would be unexpected, leading to the hypothesis that under physiologic circumstances, **RAGE** might mediate interaction with ligands distinct from AGEs. Sequential chromatography of bovine lung extract identified polypeptides with M(r) values of approximately 12,000 (p12) and approximately 23,000 (p23) which bound **RAGE**. NH2-terminal and internal protein sequence data for p23 matched that reported previously for **amphoterin**. **Amphoterin**

purified from rat brain or recombinant rat **amphoterin** bound to purified sRAGE in a saturable and dose-dependent manner, blocked by anti-**RAGE** IgG or a soluble form of **RAGE** (sRAGE). Cultured embryonic rat neurons, which express **RAGE**, displayed dose-dependent binding of 125I-**amphoterin** which was prevented by blockade of **RAGE** using antibody to the receptor or excess soluble receptor (sRAGE). A functional correlate of **RAGE**-**amphoterin** interaction was inhibition by anti-**RAGE** F(ab')2 and sRAGE of neurite formation by cortical neurons specifically on **amphoterin**-coated substrates. Consistent with a potential role for **RAGE**-**amphoterin** interaction in development, **amphoterin** and **RAGE** mRNA/antigen were co-localized in developing rat brain. These data indicate that **RAGE** has physiologically relevant ligands distinct from AGEs which are likely, via their interaction with the receptor, to participate in physiologic processes outside of the context of diabetes and accumulation of AGEs.

L4 ANSWER 3 OF 64 MEDLINE
AN 2003125715 IN-PROCESS
TI Differential effects between **amphoterin** and advanced glycation end products on colon cancer cells.
SO INTERNATIONAL JOURNAL OF CANCER, (2003 May 10) 104 (6) 722-7. Journal code: 0042124. ISSN: 0020-7136.
AU Kuniyasu Hiroki; Chihara Yoshitomo; Kondo Hideaki
AB **Amphoterin** is 1 ligand of the receptor for advanced glycation end products (**RAGE**). We studied expression of **amphoterin** and **RAGE** mRNA and proteins in colorectal carcinoma cells and investigated their associations with the invasive activities of cells exposed to advanced glycation end products (AGE). Expression of **RAGE** and **amphoterin** was examined in 4 colorectal carcinoma cell lines. All cell lines expressed both **RAGE** and **amphoterin**. The effects of **RAGE** and **amphoterin** on cell growth (MTT assay), migration (wound healing assay) and invasion (in vitro invasion assay) were tested by treatment of cells with **RAGE** and **amphoterin** antisense S-oligodeoxynucleotides (ODNs). Cell growth, migration and invasion were inhibited significantly in Colo320 and WiDr carcinoma cells treated with **RAGE** and **amphoterin** antisense S-ODNs compared with sense-treated cells. Differences in ligand activity between **amphoterin** and AGE were examined with AGE-bovine serum albumin (BSA). AGE-BSA decreased cell growth, migration and invasion of **amphoterin** antisense S-ODN-treated Colo320 and WiDr cells compared with those of cells treated with Colo320 conditioned medium. Phosphorylation of extracellular signal-regulated kinase-1/2, Rac1 and AKT and production of matrix metalloproteinase 9 were increased to a greater degree by **amphoterin** than by AGE-BSA. In contrast, production of inducible nitric oxide synthase and nuclear factor-kappaBp65 were increased to a greater degree by AGE-BSA than by **amphoterin**.

L4 ANSWER 4 OF 64 CAPLUS COPYRIGHT 2003 ACS
AN 2002:695779 CAPLUS
DN 137:232649
TI Benzimidazole derivatives as therapeutic agents
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
IN Mjalli, Adnan M. M.; Gopalaswamy, Ramesh
AB Benzimidazole derivs. having arom. groups at the 2-position, optionally sepd. from the imidazole ring by substituted alkane chain such as I are manufd. and are useful as modulators of the interaction between the receptor for advanced glycated end products (**RAGE**) and its ligands, such as advanced glycated end products (AGEs), S100/calgranulin/EN-**RAGE**, .beta.-amyloid and **amphoterin**, and for the management, treatment, control, or as an adjunct treatment for diseases in humans caused by **RAGE**. Such diseases or disease states include acute and chronic inflammation, the development of diabetic late complications such as increased vascular permeability, nephropathy, atherosclerosis, and retinopathy, the development of Alzheimer's disease, erectile dysfunction, and tumor invasion and metastasis. I was manufd. by reaction of BOC-D-(O-benzyl)tyrosine with iso-Bu chloroformate and

N,O-dimethylhydroxylamine hydrochloride at -15.degree. to room temp., redn. of the resulting amide with LiAlH4, and reaction of the resulting amino aldehyde overnight in EtOH with a diaminophenol prepd. by reaction of 3-fluoro-4-nitrophenol with BuNH2 and redn. of the resulting 3-butylamino-4-nitrophenol with SnCl2.2H2O.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002069965	A1	20020912	WO 2002-US6706	20020305
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003032663	A1	20030213	US 2002-91609	20020305

L4 ANSWER 5 OF 64 CAPLUS COPYRIGHT 2003 ACS
AN 2002:695943 CAPLUS
DN 137:216780
TI Preparation of aromatic carboxamides as modulators of receptor for advanced glycated end products (**RAGE**).
SO PCT Int. Appl., 95 pp.
CODEN: PIXXD2
IN Mjalli, Adnan M. M.; Andrews, Rob; Wysong, Christopher
AB G2R1R2CG1CONR3R4 [I; G1 = alkylene; G2 = H, alkyl, aryl, alkylaryl, amino, (substituted) imidazolyl; R1 = H, alkyl, aryl, alkylaryl; R2 = alkyl, aryl, aralkyl, etc.; R3 = H, alkyl, alkylaryl, alkoxyaryl; R4 = alkylaryl, alkoxyaryl, aryl], were prepd. I are modulators of the interaction between the receptor for advanced glycated end products (**RAGE**) and its ligands, such as advanced glycated end products (AGEs), S100/calgranulin/EN-**RAGE**, .beta.-amyloid and **amphoterin**. I are useful in treating inflammation, the development of diabetic late complications such as increased vascular permeability, nephropathy, atherosclerosis, and retinopathy, the development of Alzheimer's disease, erectile dysfunction, and tumor invasion and metastasis. Thus, 3-(3-tert-butoxyphenyl)-3-(9-fluorenylmethoxycarbonylamino)propionic acid, HTBU, diisopropylethylamine, and 2,4-bis-(3-diethylaminopropoxy)aniline (prepn. given) were stirred overnight in MeCN to give 3-(3-tert-butoxyphenyl)-3-(9-fluorenylmethoxycarbonylamino)propionic acid 2,4-bis-(3-diethylaminopropoxy)aniline amide. The latter showed IC50<0.5 .mu.M for inhibition of binding of **RAGE** to s100b.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002070473	A2	20020912	WO 2002-US6707	20020305
	WO 2002070473	A3	20021227		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2002193432	A1	20021219	US 2002-91759	20020305

L4 ANSWER 6 OF 64 CAPLUS COPYRIGHT 2003 ACS
AN 1997:719241 CAPLUS
DN 128:2367
TI **RAGE**: a receptor with a taste for multiple ligands and varied pathophysiologic states
SO Hormones and Signaling (1998), 1, 41-63
CODEN: HOSIFO
AU Schmidt, Ann Marie; Wautier, Jean-Luc; Stern, David; Yan, Shi Du
AB A review with 35 refs. The classical concept of one receptor with

specificity and high affinity for only one ligand has evolved considerably. Furthermore, there are apparently accidental but, nonetheless, pathophysiol. relevant ligands, such as intercellular adhesion mol.-1, which interacts with rhinoviruses to facilitate their entry into cells. **RAGE**, a member of the Ig of cell surface mols., shares such properties. **RAGE** interacts with different ligands, with varied implications for cellular functions, depending on the physiol. or pathophysiol. setting. For example, during normal development, **RAGE** interacts with **amphoterin**, a mol. which promotes neurite out-growth. In pathophysiol. states such as diabetes or amyloidosis obsd. in the setting of renal dialysis, **RAGE** binds non-enzymically glycated adducts of macromols. termed Advanced Glycation Endproducts, or AGEs, resulting in perturbation of multiple cellular properties. Alzheimer's disease represents a situation in which **RAGE** expression increases dramatically, and amyloid-beta peptide, thought to be crit. to the pathogenesis of neurodegeneration, is another ligand for **RAGE**. The diverse circumstances in which these varied ligands interact with **RAGE** are the subject of intense investigation to understand the distinct mechanisms that regulate the temporal and spatial expression of this receptor.

L4 ANSWER 7 OF 64 CAPLUS COPYRIGHT 2003 ACS
AN 2002:416565 CAPLUS
DN 136:383855
TI Effect of receptor for advanced glycation endproducts (**RAGE**) on invasion and metastasis of human pancreatic carcinoma cell
SO Nagoya-shiritsu Daigaku Igakkai Zasshi (2002), 53(1), 143-149
CODEN: NASDA6; ISSN: 0027-7606
AU Ohara, Eiko
AB Receptor for advanced glycation endproducts (**RAGE**) was expressed at mRNA and protein levels in human pancreatic cancer cell lines, BxPc-3, SW1990, PaCa-2 and Capan-2. Antisense **RAGE** suppressed the expression of matrix metalloproteinase 2 (MMP2) and MMP9 in those cells. Antisense **RAGE** suppressed cell invasion and cell adhesion to **laminin**-coating plate in those cells. **RAGE** participated in metastasis and invasion of human pancreatic tumor.

L4 ANSWER 8 OF 64 MEDLINE
AN 2002611052 MEDLINE
TI Receptor for advanced glycation end products (**RAGE**) signaling induces CREB-dependent chromogranin expression during neuronal differentiation.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Oct 11) 277 (41) 38635-46.
Journal code: 2985121R. ISSN: 0021-9258.
AU Huttunen Henri J; Kuja-Panula Juha; Rauvala Heikki
AB Receptor for advanced glycation end products (**RAGE**) mediates neurite outgrowth and cell migration upon stimulation with its ligand, **amphoterin**. We show here that **RAGE**-dependent changes in cell morphology are associated with proliferation arrest and changes in gene expression in neuroblastoma cells. Chromogranin B, a component of secretory vesicles in endocrine cells and neurons, was found to be up-regulated by **RAGE** signaling during differentiation of neuroblastoma cells along with the two other members of the chromogranin family, chromogranin A and secretogranin II. Ligation of **RAGE** by **amphoterin** lead to rapid phosphorylation and nuclear localization of cyclic AMP response element-binding protein (CREB), a major regulator of chromogranin expression. Furthermore, inhibition of ERK1/2-Rsk2-dependent CREB phosphorylation efficiently inhibited up-regulation of chromogranin gene expression upon **RAGE** activation. To further study the effects of **RAGE** and **amphoterin** on cellular differentiation, we stimulated embryonic stem cells expressing **RAGE** or a signaling-deficient mutant of **RAGE** with **amphoterin**. **Amphoterin** was found to promote **RAGE**-dependent neuronal differentiation of embryonic stem cells characterized by up-regulation of neuronal markers light neurofilament protein and beta-III-tubulin, activation of CREB, and increased expression of chromogranins A and B. These data suggest that **RAGE** signaling is capable of driving neuronal differentiation involving CREB activation and induction of chromogranin expression.

L4 ANSWER 9 OF 64 CAPLUS COPYRIGHT 2003 ACS
AN 2001:724797 CAPLUS
DN 136:18922
TI The multiligand receptor **RAGE** as a progression factor amplifying immune and inflammatory responses
SO Journal of Clinical Investigation (2001), 108(7), 949-955
CODEN: JCINAO; ISSN: 0021-9738
AU Schmidt, Ann Marie; Yan, Shi Du; Yan, Shi Fang; Stern, David M.
AB A review discussing the diverse functions of the multi-ligand receptor **RAGE**. It discusses the involvement of **RAGE** in diabetes, cellular dysfunction in the amyloidoses, propagation of the immune/inflammatory response, and in function of **amphoterin**.

(FILE 'HOME' ENTERED AT 16:40:54 ON 27 MAR 2003)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 16:41:02 ON 27 MAR 2003

L1 3464 S (RECEPTOR FOR ADVACNCED GLYCATION ENDPRODDUCT?) OR RAGE
L2 137 S L1 AND (LAMININ OR FIBRONECTIN OR AMPHOTERIN OR CADERIN OR IN
L3 64 DUP REM L2 (73 DUPLICATES REMOVED)
L4 64 FOCUS L3 1-
L5 14 S L4 AND PY<=1998
L6 14 SORT L5 PY

=> d an ti so au ab pi l4 1

L4 ANSWER 1 OF 64 CAPLUS COPYRIGHT 2003 ACS
AN 1999:691229 CAPLUS
DN 131:317761
TI Inhibition of tumor invasion or spreading based on a soluble receptor for advanced glycation endproducts
SO PCT Int. Appl., 88 pp.
CODEN: PIXXD2
IN Schmidt, Ann Marie; Stern, David
AB The present invention provides for a method for inhibiting tumor invasion or metastasis in a subject which comprises administering to the subject a therapeutically effective amt. of a form of sol. receptor for advanced glycation endproducts (**RAGE**). Interruption of cellular **RAGE**-extracellular matrix (**amphoterin** and/or similar structures) interaction appears to be at least one mechanism by which sRAGE limits tumor growth. The present invention also provides a method for evaluating the ability of an agent to inhibit tumor invasion in a local cellular environment which comprises: (a) admixing with cell culture media an effective amt. of the agent; (b) contacting a tumor cell in cell culture with the media from step (a); (c) detg. the amt. of spreading of the tumor cell culture, and (d) comparing the amt. of spreading of the tumor cell culture detd. in step (c) with the amt. detd. in the absence of the agent, thus evaluating the ability of the agent to inhibit tumor invasion in the local cellular environment. The present invention also provides a pharmaceutical compn. which comprises a therapeutically effective amt. of the agent evaluated in the aforementioned method and a pharmaceutically acceptable carrier.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9954485	A1	19991028	WO 1999-US8427	19990416
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6465422	B1	20021015	US 1998-62365	19980417
CA 2325573	AA	19991028	CA 1999-2325573	19990416
AU 9934957	A1	19991108	AU 1999-34957	19990416
EP 1071794	A1	20010131	EP 1999-916699	19990416
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002512038	T2	20020423	JP 2000-544814	19990416
US 2002177550	A1	20021128	US 2001-851071	20010508

10 ANSWER 1 OF 69 CAPLUS COPYRIGHT 2003 ACS
AN 1996:748350 CAPLUS
DN 126:17792
TI Kidney carcinoma **tumor** rejection antigen **RAGE** TRA cDNA sequences, antigen recombinant production, and **cancer** diagnosis and treatment
SO PCT Int. Appl., 105 pp.
CODEN: PIXXD2
IN Gaugler, Beatrice; Van Den Eynde, Benoit; Schrier, Peter; Brouwenstijn, Nathalie; Boon-Falleur, Thierry
AB The invention describes the **RAGE tumor** rejection antigen precursor family, including nucleic acids encoding such **tumor** rejection antigen precursors, **tumor** rejection antigen peptides or precursors thereof and antibodies relating thereto. Methods and products also are provided for diagnosing and treating conditions characterized by expression of a **RAGE tumor** rejection antigen precursor.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 9629409	A2	19960926	WO 1996-US4037	19960321	<--
WO 9629409	A3	19961107			
W: AU, CA, CN, JP, NO, NZ					
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
US 5939526	A	19990817	US 1995-530569	19950920	
AU 9654298	A1	19961008	AU 1996-54298	19960321	<--
AU 705768	B2	19990603			
EP 815229	A2	19980107	EP 1996-911399	19960321	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 11506904	T2	19990622	JP 1996-528658	19960321	

L10 ANSWER 2 OF 69 CAPLUS COPYRIGHT 2003 ACS
AN 1999:518306 CAPLUS
DN 131:169277
TI Isolated **RAGE**-1 derived peptides which complex with HLA-B7 molecules and uses thereof
SO U.S., 32 pp., Cont.-in-part of U.S. Ser. No. 408,015.
CODEN: USXXAM
IN Gaugler, Beatrice; Vanden, Eynde Benoit; Schrier, Peter; Brouwenstijn, Nathalie; Boon-Falleur, Thierry
AB The invention describes the **RAGE tumor** rejection antigen precursor family, including nucleic acids encoding such **tumor** rejection antigen precursors, **tumor** rejection antigen peptides or precursors thereof and antibodies relating thereto. Methods and products also are provided for diagnosing and treating conditions characterized by expression of a **RAGE tumor** rejection antigen precursor.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI US 5939526	A	19990817	US 1995-530569	19950920	
ZA 9602280	A	19960828	ZA 1996-2280	19960320	<--
CA 2211448	AA	19960926	CA 1996-2211448	19960321	<--
WO 9629409	A2	19960926	WO 1996-US4037	19960321	<--
WO 9629409	A3	19961107			
W: AU, CA, CN, JP, NO, NZ					
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
AU 9654298	A1	19961008	AU 1996-54298	19960321	<--
AU 705768	B2	19990603			
EP 815229	A2	19980107	EP 1996-911399	19960321	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
CN 1179180	A	19980415	CN 1996-192650	19960321	<--
JP 11506904	T2	19990622	JP 1996-528658	19960321	

L15 ANSWER 4 OF 1211 CAPLUS COPYRIGHT 2003 ACS
AN 1988:527128 CAPLUS
DN 109:127128
TI **Tumor** necrosis factor **inhibits** collagen and **fibronectin** synthesis in human dermal fibroblasts
SO FEBS Letters (**1988**), 236(1), 47-52
CODEN: FEBLAL; ISSN: 0014-5793
AU Mauviel, A.; Daireaux, M.; Redini, F.; Galera, P.; Loyau, G.; Pujol, J. P.
AB **Tumor** necrosis factor (TNF) caused **inhibition** of collagen prodn. by confluent **cultures** of human dermal fibroblasts in a dose-dependent manner. Concomitant increase of prostaglandin E2 release was obsd. as a result of TNF-induced cell activation. However, a blockade of the cyclooxygenase pathway of arachidonate metab. by indomethacin did not abrogate the **inhibitory** effect of TNF on collagen synthesis, suggesting that this effect could be independent of prostaglandin metab. Gel electrophoresis of the newly synthesized macromols. from the **culture** media showed that both type I and type III collagens as well as **fibronectin** were affected by the **inhibition**. Electrophoresis of cell layer-assocd. proteins demonstrated that the redn. in amts. of collagen and **fibronectin** in the medium did not result from an intracellular accumulation of these macromols. Prodn. of procollagens was reduced in parallel to that of collagens, suggesting that the effect of TNF is exerted before the processing steps of procollagens. Thus, TNF could play a role in modulation of matrix deposition by fibroblasts during inflammatory processes.

L15 ANSWER 5 OF 1211 CAPLUS COPYRIGHT 2003 ACS
AN 1987:475396 CAPLUS
DN 107:75396
TI **Laminin** stimulates the attachment, spread and incorporation of 3H-TdR into **cancer** cells
SO Shengwu Huaxue Zazhi (**1987**), 3(3), 261-9
CODEN: SHZAE4; ISSN: 1000-8543
AU Zhou, Rouli; Gao, Suying; Wang, Su; Ma, Kangtao; Wang, Xinmin; Sun, Quan; Jing, Yueying; Zhang, Sha; Liang, Limin; Lin, Min
AB The attachment to basement membranes and the proliferation on defined matrixes of **cancer** cells are of fundamental importance in the processes of invasion and metastasis. The effects of **laminin** on **cancer** cell attachment, spread, and [3H]TdR incorporation was studied. The attachment of cells was quantitated by measuring LDH activity. **Laminin** markedly stimulated the attachment and spread of mouse S180-V sarcoma cells and B16-MBK melanoma cells in **culture** on solid support. **Fibronectin**, but not other glycoproteins such as egg albumin, showed similar stimulation of **cancer** cell attachment. Furthermore, cell attachment to **laminin** or **fibronectin** was specifically **inhibited** by antibody against **laminin** or **fibronectin**, resp. These results indicate that the role of **laminin** was specific. The surface of attached cells was obsd. under scanning electron microscope. **Cancer** cells attached to the surface of bare glass were round with numerous ruffles and microvilli. In contrast, those attached to the **laminin**-coated glass surface appeared polygonal and flat in morphol., with fewer ruffles and microvilli. In addn., the incorporation of [3H]TdR into **cancer** cells attached to **laminin** matrixes was substantially increased. The role of **laminin** in the invasion and metastasis of **cancer** cells is discussed.

(FILE 'HOME' ENTERED AT 16:40:54 ON 27 MAR 2003)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 16:41:02 ON 27 MAR 2003

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L1          3464 S (RECEPTOR FOR ADVACNCED GLYCATION ENDPRODDUCT?) OR RAGE
L2           137 S L1 AND (LAMININ OR FIBRONECTIN OR AMPHOTERIN OR CADERIN OR IN
L3            64 DUP REM L2 (73 DUPLICATES REMOVED)
L4            64 FOCUS L3 1-
L5            14 S L4 AND PY<=1998
L6            14 SORT L5 PY
L7           333 S L1 AND (CANCER OR TUMOR OR NEOPLAS? TUMOUR)
L8           180 DUP REM L7 (153 DUPLICATES REMOVED)
L9            69 S L8 AND PY<=1998
L10           69 FOCUS L9 1-
L11        33209 S (CANCER OR TUMOR OR NEOPLAS? OR TUMOUR) (L) (LAMININ OR FIBRO
L12        10728 S L11 AND INHIBIT?
L13         2282 S L12 AND (CULTURE OR IN(W)VITRO)
L14         1211 S L13 AND PY<=1997
L15         1211 FOCUS L14 1-
L16           63 S (CANCER OR TUMOR OR NEOPLAS? OR TUMOUR) (L) AMPHOTERIN
L17           28 DUP REM L16 (35 DUPLICATES REMOVED)
L18           28 SORT L17 PY
L19            4 S L18 AND PY<=1998
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=> d an ti so au ab pi l19 1-4

L19 ANSWER 1 OF 4 MEDLINE

AN 97433100 MEDLINE

TI Differential messenger RNA and protein expression of the receptor for advanced glycosylated end products in normal lung and non-small cell lung carcinoma.

SO CANCER RESEARCH, **(1997 Sep 1)** 57 (17) 3669-71.
Journal code: 2984705R. ISSN: 0008-5472.

AU Schraml P; Bendik I; Ludwig C U

AB The receptor for advanced glycosylated end products (RAGE), a member of the immunoglobulin superfamily, was one of the cDNA subtraction clones that was found to be differentially expressed in human lung and the corresponding **tumor** tissue. In nine additional matched normal/**tumor** pairs, a strongly reduced or missing expression, not only on a transcriptional level but also on a protein level, was demonstrated in the non-small cell lung carcinoma tissue. Because **amphoterin**, a physiological ligand of RAGE that is highly expressed in the lung, mediates cell differentiation via RAGE, a down-regulation of the receptor may be considered as a critical step in lung **tumor** formation. Furthermore, we determined the complete reading frame of RAGE.

(FILE 'HOME' ENTERED AT 16:40:54 ON 27 MAR 2003)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 16:41:02 ON 27 MAR 2003

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L1          3464 S (RECEPTOR FOR ADVACNCED GLYCATION ENDPRODDUCT?) OR RAGE
L2           137 S L1 AND (LAMININ OR FIBRONECTIN OR AMPHOTERIN OR CADERIN OR IN
L3            64 DUP REM L2 (73 DUPLICATES REMOVED)
L4            64 FOCUS L3 1-
L5            14 S L4 AND PY<=1998
L6            14 SORT L5 PY
L7           333 S L1 AND (CANCER OR TUMOR OR NEOPLAS? TUMOUR)
L8           180 DUP REM L7 (153 DUPLICATES REMOVED)
L9            69 S L8 AND PY<=1998
L10           69 FOCUS L9 1-
L11        33209 S (CANCER OR TUMOR OR NEOPLAS? OR TUMOUR) (L) (LAMININ OR FIBRO
L12        10728 S L11 AND INHIBIT?
L13         2282 S L12 AND (CULTURE OR IN(W)VITRO)
L14         1211 S L13 AND PY<=1997
L15         1211 FOCUS L14 1-
L16           63 S (CANCER OR TUMOR OR NEOPLAS? OR TUMOUR) (L) AMPHOTERIN
L17           28 DUP REM L16 (35 DUPLICATES REMOVED)
L18           28 SORT L17 PY
L19            4 S L18 AND PY<=1998
L20          115 S L1 AND AMPHOTERIN
L21           48 DUP REM L20 (67 DUPLICATES REMOVED)
L22            9 S L21 AND PY<=1998
L23            9 SORT L22 PY

=> d an ti so au ab pi l23 1-9

L23  ANSWER 1 OF 9     MEDLINE
AN   96029671     MEDLINE
TI   The receptor for advanced glycation end products (RAGE) is a
     cellular binding site for amphoterin. Mediation of neurite
     outgrowth and co-expression of rage and amphoterin in
     the developing nervous system.
SO   JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Oct 27) 270 (43)
     25752-61.
     Journal code: 2985121R. ISSN: 0021-9258.
AU   Hori O; Brett J; Slattery T; Cao R; Zhang J; Chen J X; Nagashima M; Lundh
     E R; Vijay S; Nitecki D; +
AB   The receptor for advanced glycation end products (RAGE), a
     newly-identified member of the immunoglobulin superfamily, mediates
     interactions of advanced glycation end product (AGE)-modified proteins
     with endothelium and other cell types. Survey of normal tissues
     demonstrated RAGE expression in situations in which accumulation
     of AGEs would be unexpected, leading to the hypothesis that under
     physiologic circumstances, RAGE might mediate interaction with
     ligands distinct from AGEs. Sequential chromatography of bovine lung
     extract identified polypeptides with M(r) values of approximately 12,000
     (p12) and approximately 23,000 (p23) which bound RAGE.
     NH2-terminal and internal protein sequence data for p23 matched that
     reported previously for amphoterin. Amphoterin
     purified from rat brain or recombinant rat amphoterin bound to
     purified sRAGE in a saturable and dose-dependent manner, blocked by anti-
     RAGE IgG or a soluble form of RAGE (sRAGE). Cultured
     embryonic rat neurons, which express RAGE, displayed
     dose-dependent binding of 125I-amphoterin which was prevented by
     blockade of RAGE using antibody to the receptor or excess
     soluble receptor (sRAGE). A functional correlate of RAGE-
     amphoterin interaction was inhibition by anti-RAGE
     F(ab')2 and sRAGE of neurite formation by cortical neurons specifically on
     amphoterin-coated substrates. Consistent with a potential role for
     RAGE-amphoterin interaction in development,
     amphoterin and RAGE mRNA/antigen were co-localized in
     developing rat brain. These data indicate that RAGE has
     physiologically relevant ligands distinct from AGEs which are likely, via
     their interaction with the receptor, to participate in physiologic
     processes outside of the context of diabetes and accumulation of AGEs.
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L23 ANSWER 2 OF 9 SCISEARCH COPYRIGHT 2003 ISI (R)
AN 95:201535 SCISEARCH
TI THE RECEPTOR FOR ADVANCED GLYCATION ENDPRODUCTS (**RAGE**) IS A CELL-SURFACE RECEPTOR FOR **AMPHOTERIN** IN THE DEVELOPING CENTRAL-NERVOUS-SYSTEM (CNS) TO PROMOTE NEURITE OUTGROWTH
SO FASEB JOURNAL, (**09 MAR 1995**) Vol. 9, No. 3, Part 1, pp. A382. ISSN: 0892-6638.
AU HORI O (Reprint); CAO R; BRETT J; SLATTERY T; NAGASHIMA M; NITECKI D; MORSER J; STERN D; SCHMIDT A M

L23 ANSWER 3 OF 9 MEDLINE
AN 97433100 MEDLINE
TI Differential messenger RNA and protein expression of the receptor for advanced glycosylated end products in normal lung and non-small cell lung carcinoma.
SO CANCER RESEARCH, **(1997 Sep 1)** 57 (17) 3669-71. Journal code: 2984705R. ISSN: 0008-5472.
AU Schraml P; Bendik I; Ludwig C U
AB The receptor for advanced glycosylated end products (**RAGE**), a member of the immunoglobulin superfamily, was one of the cDNA subtraction clones that was found to be differentially expressed in human lung and the corresponding tumor tissue. In nine additional matched normal/tumor pairs, a strongly reduced or missing expression, not only on a transcriptional level but also on a protein level, was demonstrated in the non-small cell lung carcinoma tissue. Because **amphoterin**, a physiological ligand of **RAGE** that is highly expressed in the lung, mediates cell differentiation via **RAGE**, a down-regulation of the receptor may be considered as a critical step in lung tumor formation. Furthermore, we determined the complete reading frame of **RAGE**.

L23 ANSWER 4 OF 9 MEDLINE
AN 97184302 MEDLINE
TI The receptor for advanced glycation end products mediates the chemotaxis of rabbit smooth muscle cells.
SO DIABETES, **(1997 Mar)** 46 (3) 463-72. Journal code: 0372763. ISSN: 0012-1797.
AU Higashi T; Sano H; Saishoji T; Ikeda K; Jinnouchi Y; Kanzaki T; Morisaki N; Rauvala H; Shichiri M; Horiuchi S
AB Long-term incubation of proteins with glucose leads to advanced glycation end products (AGEs) with fluorescence and a brown color. We recently demonstrated immunologically the intracellular AGE accumulation in smooth muscle cell (SMC)-derived foam cells in advanced atherosclerotic lesions. To understand the mechanism of AGE accumulation in these foam cells, we have now characterized the interaction of AGE proteins with rabbit-cultured arterial SMCs. In experiments at 4 degrees C, 125I-labeled AGE-bovine serum albumin (AGE-BSA) showed a dose-dependent saturable binding to SMCs with an apparent dissociation constant (Kd) of 4.0 microg/ml. In experiments at 37 degrees C, AGE-BSA underwent receptor-mediated endocytosis and subsequent lysosomal degradation. The endocytic uptake of 125I-AGE-BSA was effectively inhibited by unlabeled AGE proteins such as AGE-BSA and AGE-hemoglobin, but not by acetylated LDL and oxidized LDL, well-known ligands for the macrophage scavenger receptor (MSR). Moreover, the binding of 125I-AGE-BSA to SMCs was affected neither by **amphoterin**, a ligand for one type of the AGE receptor, named **RAGE**, nor by 2-(2-furoyl)-4(5)-(2-furanyl)-1H-imidazole-hexanoic acid-BSA, a ligand for the other AGE receptors, p60 and p90. This indicates that the endocytic uptake of AGE proteins by SMCs is mediated by an AGE receptor distinct from MSR, **RAGE**, p60, and p90. To examine the functional role of this AGE receptor, the migratory effects of AGE-BSA on these SMCs were tested. Incubation with 1-50 microg/ml of AGE-BSA for 14 h resulted in significant dose-dependent cell migration. The AGE-BSA-induced SMC migration was chemotactic in nature and was significantly inhibited (approximately 80%) by an antibody against transforming growth factor-beta (TGF-beta), and the amount of TGF-beta secreted into the culture medium from SMC by AGE-BSA was sevenfold higher than that of control, indicating that TGF-beta is involved in the AGE-induced SMC chemotaxis. These data suggest that AGE may play a role in SMC migration in advanced atherosclerotic lesions.

L23 ANSWER 5 OF 9 MEDLINE

AN 1999030344 MEDLINE

TI Sp1-binding elements in the promoter of **RAGE** are essential for **amphoterin**-mediated gene expression in cultured neuroblastoma cells.

SO JOURNAL OF BIOLOGICAL CHEMISTRY, **(1998 Nov 20)** 273 (47) 30870-8. Journal code: 2985121R. ISSN: 0021-9258.

AU Li J; Qu X; Schmidt A M

AB Receptor for AGE (**RAGE**) and the polypeptide **amphoterin** are highly expressed and co-localized in neurons of the developing central nervous system of the rat. In vitro, the interaction of **amphoterin** with neuronal **RAGE** induces neurite outgrowth. We tested the hypothesis that interaction of **amphoterin** with neuronal cells enhances **RAGE** expression, thereby providing a mechanism by which **amphoterin**-mediated regulation of **RAGE** might contribute to promotion of neurite growth and spreading. Incubation of cultured neuroblastoma cells with **amphoterin** resulted in increased transcription and translation of **RAGE**, a process largely inhibited in the presence of anti-**RAGE** IgG but not by nonimmune IgG. To begin to delineate molecular mechanisms underlying these findings, we identified multiple putative binding elements within the 5'-flanking region of the **RAGE** gene for Sp1, a transcription factor that has been critically linked to the process of normal development. DNase I footprinting and electrophoretic mobility shift assays demonstrated multiple functional Sp1-binding sites within the region -245 to -40 of the **RAGE** promoter. Transient transfection of cultured SK-N-SH neuroblastoma cells with chimeric 5'-deletion constructs linked to luciferase reporter revealed that the region containing Sp1-binding elements did not contribute uniquely to basal expression of the **RAGE** gene. Simultaneous mutation of the multiple Sp1-binding elements in this region did not affect basal promoter function; however, promoter responsiveness to **amphoterin** was markedly attenuated. These results point to Sp1-dependent mechanisms underlying **amphoterin**-mediated increases in **RAGE** expression in neuroblastoma cells and further link **amphoterin-RAGE** interaction to development of the nervous system.